UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 9, 2007

MEMORANDUM

SUBJECT: Glutaraldehyde: Review of an Odor and Chemesthesis Human Study.

DP Barcode: D327465
TXR: 0054625
PC Code: 043901

FROM: Elissa Reaves, Ph.D., Toxicologist 7/9/07
Reregistration Branch 2
Health Effects Division (7509P)

THROUGH: William Hazel, Ph.D., Branch Chief
Reregistration Branch 2
Health Effects Division (7509P)

TO: Michelle Centra, Chemical Review Manager
RMB2, Antimicrobials Division (7510P)

I. Conclusions:

The two-phase human study provides useful range-finding and threshold information but does not provide useful information for longer durations and/or repeated exposures. Since this two-phase odor and chemesthesis study identified odor, eye, and nasal thresholds which may inform very brief exposures to this chemical, the study is classified as **ACCEPATBLE/NON-GUIDELINE**.

II. Action Requested:

The Antimicrobials Division (AD) of the Office of Pesticide Programs (OPP) requested that the odor and chemesthesis human study (MRID 47019801) be reviewed and a Data Evaluation Record (DER) generated in support of the Reregistration Eligibility Decision (RED) for glutaraldehyde.

III. Study Results:

Phase I results: Odor was 3 orders of magnitude more sensitive than eye and nasal detection. Nasal detection was more sensitive than eye detection in female subjects. Female subjects, however, failed to lateralize (left or right) feeling of glutaraldehyde in the nose.

Phase II results: A LOAEL was not established in this phase. The NOAEL for perception of irritation after 15 minutes is > 100 ppb.

Please refer to the DER for further details.

2

EPA Reviewer: Elissa Reaves, Ph.D. **Signature:** Elissa Reaves
Reregistration Branch 2 (RRB2), HED **Date** 6/27/07
EPA Secondary Reviewer: _____ **Signature:** _____
Reregistration Branch, Antimicrobial Division **Date** 6/27/07

TXR#: 0054625

DATA EVALUATION RECORD

STUDY TYPE: Human Odor and Chemesthesis; Non-guideline

PC CODE: 043901 **DP BARCODE:** 327465

TEST MATERIAL (PURITY): Glutaraldehyde, 26.1%

SYNONYMS: 1,5-Pentanedial; 1,2-Diformylpropane; Glutaral dialdehyde; Glutaric dialdehyde

CITATION: Cain W., R. Schmidt, A. Jalowayski, et al (2006) Odor and Chemesthesis from Exposure to Glutaraldehyde Vapor. Chemosensory Perception Laboratory, University of California, San Diego. Laboratory Project Study ID K-020301-123, December 12, 2006. MRID 47019801. Unpublished.

SPONSOR: Dow Chemical Company and BASF Corporation

EXECUTIVE SUMMARY: In a non-guideline human study, 50 healthy female volunteers (18 to 35 years of age) were exposed to a range of vapor concentrations and durations in a controlled laboratory setting for derivation of odor and chemesthesis thresholds for the eye, nose, and throat (MRID 47019801). The subjects were representative in regards to gender, age, and ethnicity of the workforce most commonly exposed to glutaraldehyde (i.e., healthcare workers performing cold sterilization); and participated in both phases of the study. Power analyses were evaluated post hoc and reported for Phase I and Phase II of the study. Pyschometric functions were analyzed for slopes and intercepts, with slope indicative of intra-subject variability and intercept indicative of absolute sensitivity, and inter-subject variability. An ANOVA was performed on confidence scores in Phase II. An independent AD analysis was performed to determine the number of subjects initially and consistently identifying glutaraldehyde (beyond chance) via odor, eye, or nose in Phase I.

- **Phase I:** Vapor Delivery Device

The objective of Phase I was the identification of glutaraldehyde by odor (both nostrils, single sniff), eye feel (one eye, approximately 25 seconds), and nasal feel (one nostril, approximately 7 seconds) over a range of concentrations.

  - Odor Detection: Single sniff exposure from a cone (5 seconds) at 0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, or 4.950 ppb

- Ocular Detection: A single eye exposure from a cone (25 seconds) at 229, 343, 514, or 772 ppb
- Nasal Localization: Single sniff exposure for localization of feel in right or left nostril (5 seconds) at 0, 229, 344, 515, or 772 ppb

- **Phase II:** Environmental Chamber

Phase II examined the potential of glutaraldehyde to induce sensory irritation in the eyes, nose, or throat of the subject over the course of 15 minutes. Confidence scores of feeling irritation as time progressed were captured for the eyes, nose, and throat.

- A 15-minute exposure each to 0, 35, 50, 75, and 100 ppb glutaraldehyde, 10 ppm heptane (odor control), and blank (air)

- **Phase III:** Not conducted

A third phase, intended to evaluate physiological changes to irritative exposures of glutaraldehyde, was not performed due to the lack of an irritation response to glutaraldehyde observed at any of the test concentrations in Phase II.

Phase I Results

Study Report Results: According to the study report, subjects detected odor on half of trials above chance by a concentration of 0.5 ppb and achieved virtually perfect detection at or not far above 1 ppb. The point of 50% detection for odor was 0.3 ppb while eye and nose occurred at 390 ppb and 470 ppb, respectively. It should be noted, however, that the analysis for determining these medians was not presented in the study report.

Psychometric functions were presented to illustrate how detection/localization fluctuated over time, i.e., from trial to trial. For odor, fluctuation occurred over a 100 to 1 range of concentrations. For chemesthesis, fluctuation occurred over a 10 to 1 range.

AD Independent Analysis (see Appendix A for details):

Odor: An independent analysis by the Antimicrobials Division (AD) indicates approximately 23% (10 of 43) of subjects positively identified the odor (green apple) of glutaraldehyde initially at 0.039 ppb and consistently to 4.950 ppb. At 0.15 ppb, 23 of 43 subjects (53%) identified the odor of glutaraldehyde. At the highest concentration (4.95 ppb), 96% (41 of 43) of subjects detected odor. However, 2 subjects failed to identify odor up to 4.95 ppb. A simple tally of the 50th percentile suggests the odor median is 0.15 ppb.

Ocular Detection: Approximately 39% (16 of 41) of subjects positively identified eye feel beyond chance initially at 229 ppb and consistently to 772 ppb. One subject failed to detect eye feel up to 772 ppb. However, 98% (10 of 41) identified glutaraldehyde in the eye at 772 ppb. The 50th percentile is 343 ppb based on the simple tally method.

Nasal Localization: For nasal chemesthesis, 77.5% (31 of 40) of subjects positively identified glutaraldehyde in the nose at the lowest concentration of 229 ppb. All subjects identified glutaraldehyde in the nose at 772 ppb. The 50th percentile is therefore 229 ppb.

TABLE 1. Phase 1 results for odor, eye, and nasal threshold of glutaraldehyde				
Exposure Concentration	**Exposure Duration**	**Number of Participants**	**Median Threshold in Report**	**AD Independent Analysis**
Odor Detection				
0, 0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, and 4.950 ppb	>5 seconds "sniff"	43	Odor median 0.3 ppb	23% at 0.039 ppb (10 of 43); 2 non-detecting; Median 0.15 ppb
Ocular Feel				
0, 229, 343, 514, and 772 ppb	25 seconds	41	Ocular median 390 ppb	39% at 229 ppb (16 of 41); 1 non-detecting; Median 343 ppb
Nasal Localization				
0, 229, 343, 514, and 772 ppb	>5 seconds "sniff"	40	Nasal median 470 ppb*	77.5% at 229 ppb (31 of 40); 0 non-detecting; Median 229 ppb

*The 50th percentile of nasal detection is reported as 470 ppb on page 23 and 440 on page 25.

Summary Results Phase I: Odor was 3 orders of magnitude more sensitive than eye and nasal detection. Nasal detection was more sensitive than eye detection in female subjects. Female subjects, however, failed to lateralize (left or right) feeling of glutaraldehyde in the nose.

Summary Results Phase II: In general, female subjects failed to positively detect glutaraldehyde either in the eyes, nose, or throat over the concentrations and duration (15 minutes) investigated. For the eye, 86% of subjects (43 of 50) failed to detect, while 66% (33 of 50) and 84% (42 of 50) failed to detect in the nose and throat, respectively. One subject did detect initially at the lowest concentration and consistently to the highest concentration for the eye, nose, and throat. As a group, however, there was no concentration-response relationship for the eyes, nose, or throat. Examination of the confidence scores suggests that the nose may be more sensitive than the eyes which may be more sensitive than the throat, which is consistent with findings in Phase I. A concentration that 50% of the subjects could detect (eye, nose, or throat) was not identified. **A LOAEL was not established in this phase. The NOAEL for perception of irritation after 15 minutes is > 100 ppb.**

This study provides useful range-finding and threshold information but does not provide useful information for longer durations and/or repeated exposures. Since this two-phase odor and chemesthesis study identified odor, eye, and nasal thresholds which may inform very brief exposures to this chemical, the study is classified as **ACCEPTABLE/NON-GUIDELINE.**

COMPLIANCE: Signed and dated GLP, Internal and External Quality Assurance, and No Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** Glutaraldehyde (26.1%)

Description:	Liquid, green apple odor
Molecular Weight:	100.13
Lot#:	001197
Purity:	26.1% a.i. in water
Compound stability:	Not reported
CAS # for TGAI:	111-30-8
Structure:	

Source: Chemfinder.com

2. **Vehicle and/or Positive Control:** Air as blank, heptane (10 ppm) as odor control.

3. **Study Rationale For Concentration And Duration:**
The study report cited reports by Curran et al. (1996); Di Stefano et al., (1999), Gannon et al., 1995, and Quirce et al., (1999) that stated incidences of asthma-like responses were observed in some workers from exposure to glutaraldehyde in occupational settings. These reviews were not the references that were relied upon for basing concentration and duration for the human sensory study. Instead, they were used as a flag to the study authors to take precautions for severe adverse reactions to glutaraldehyde vapor. Furthermore, the study report cites Ballantyne (1995) as providing toxicity information by different routes of exposure and durations ranging from acute to chronic. The known effects in humans from overexposure to glutaraldehyde were listed as irritancy to the eye, skin, and respiratory tract. However, the available data on glutaraldehyde and human exposure was considered deficient in determining a concentration or duration of exposure; therefore, this study was to establish odor and feel thresholds for glutaraldehyde.

The study report highlighted that the chosen duration focused on very brief exposures (Phase I) and more extended exposures (Phase II). The extended Phase II scenarios focused on concentrations determined from Phase I results.

4. **Subjects:**

Healthy Human Volunteers:
Total of Individuals: 50 total females (majority of subjects likely recruited from college campuses via fliers, pg 226)
Age: 18 to 35 years

Study Dates: Study dates not provided in report. In the appendices, however, calibration curve tables for Phase I indicate dates from August 13, 2001 to February 18, 2002; and Phase II dates from January 15, 2003 to April 23, 2003.

Each subject was given a Subject Identification Number (SID) based on date of birth, sequential participation, etc.

Subject's Bill of Rights and Informed Consent:
Subjects received and signed an Experimental Subject's Bill of Rights and Informed Consent Form. (pg 227-233)

Screening of Subjects:
All study subjects were recruited from the general population by fliers and were initially phone screened for smoking (tobacco or marijuana in the past year), excessive alcohol consumption (≥3 drinks day/year), drug use (excluding birth control), chronic or recent acute illness, respiratory allergies, exposure to glutaraldehyde occupationally, and asthma. Individuals that passed the initial phone screen were clinically evaluated for signs of illness or abnormalities to upper respiratory tract. Signed consent forms, protocols, and Human Review Board approval were provided. During the screening process, the only question that subjects could answer "yes" to and still remain in consideration for inclusion concerned allergies. Some dormant upper respiratory allergies did not disqualify the subject per se from further consideration. If the person agreed to participate, she signed the informed consent form and took a brief odor identification test to assess normality of smell.

A screening packet with forms used to assess the fitness of each participant in the study was generated (subject screening packet is provided in Appendix H pp. 384-395 of report). Packets contained subject contact information, symptom evaluation forms, a pregnancy test, and other forms for documentation of screening parameters.
A medical history concerning the upper respiratory and ocular systems, followed by a clinical examination of the nose, oral cavity, throat, eyes, and sense of smell, was obtained from each individual. Additionally, each individual underwent a nasal resistance measurement, airway function testing by spirometry, a cytological examination of the upper turbinate, and a pregnancy test. After passing the tests for customary clinical criteria and pregnancy, the resulting 50 nonsmoking females, ranging in age from 18-35 years, were used for both phases. Young women were chosen as the most sensitive part of the normal adult population, since women and younger adults exhibit greater chemesthetic sensitivity as compared to men and older adults, respectively (Garcia Medina and Cain, 1982, Dunn et al., 1982, Stevens et al., 1982). Furthermore, glutaraldehyde is widely used in the healthcare industry as a cold sterilant of medical and surgical equipment and the demographics of healthcare workforce indicate that healthcare

workers are mainly women. In addition, the participants were an ethnically diverse group of subjects (10% African-American, 20% Asian-American or Pacific Islander, 46% Caucasian Non-Hispanic, and 24% Caucasian Hispanic) in order to assess associations of sensitivity to glutaraldehyde with ethnicity. The same subjects participated in Phase I and Phase II.

5. Test Apparatus:

An 8-station vapor delivery devise (VDD) was used for Phase I of the study. Concentrations for subject exposure were generated by metering either liquid glutaraldehyde or a heptane solution into a heated chamber (150°C), where it was vaporized and swept by a stream of nitrogen into either a Vapor Delivery Devise (VDD) in Phase I, or an environmental chamber in Phase II.

Figures 1 and 2 (see below) from the final report (pp. 18 and 204) depict a schematic of the VDD and the environment chamber, respectively. The vapor-phase concentrations are presented in Table 2 below.

TABLE 2. Concentration of glutaraldehyde in VDD [a]

Nominal (ppb)	Actual (mean ppb±SD; CV%)	%	Phase	Section
2.48	1.8±0.3 (15.2)	74.0	Phase I	Odor Detection
4.95	3.7±0.3 (7.8)	75.2	Phase I	Odor Detection
4.95	3.3±0.3 (8.0)	67.6	Phase I	Odor Detection
4.95	4.9±1.0 (19.9)	98.1	Phase I	Odor Detection
4.95	4.6±0.3 (6.8)	92.2	Phase I	Odor Detection
4.95	4.7±0.1 (3.0)	95.2	Phase I	Odor Detection
4.95	5.5±0.2 (4.0)	111.6	Phase I	Odor Detection
4.95	5.3±0.8 (15.4)	106.7	Phase I	Odor Detection
4.95	4.5±0.2 (5.0)	91.8	Phase I	Odor Detection
4.95	4.3±0.0 (0.6)	86.8	Phase I	Odor Detection
4.95	4.8±0.8 (16.2)	96.4	Phase I	Odor Detection
4.95	4.3±0.0 (0.9)	87.8	Phase I	Odor Detection
4.95	5.0±0.3 (7.0)	100.4	Phase I	Odor Detection
4.95	4.5±1.4 (32.2)	90.2	Phase I	Odor Detection
9.90	9.3±0.2 (2.5)	94.2	Phase I	Odor Detection
72	59.6±2.3 (3.8)	82.8	Phase I	Ocular Detection
108	96.7±6.1 (6.3)	89.6	Phase I	Ocular Detection
108	102.1±5.7 (5.5)	94.6	Phase I	Nasal Localization
243	225.9±22.2 (9.8)	93.0	Phase I	Ocular Detection
243	261.3±33.5 (12.8)	107.5	Phase I	Ocular Detection
243	234.4±15.0 (6.4)	96.4	Phase I	Ocular Detection
243	265.4±3.9 (1.5)	109.2	Phase I	Ocular Detection
243	247.2±43.2 (17.5)	101.7	Phase I	Ocular Detection
243	234.9±48.1(20.5)	96.7	Phase I	Nasal Localization
243	244.8±40.6 (16.6)	100.7	Phase I	Nasal Localization
243	231.3±41.0 (17.7)	95.2	Phase I	Nasal Localization
243	231.1±28.4 (12.3)	95.1	Phase I	Ocular Detection
243	245.8±58.8 (23.9)	101.1	Phase I	Nasal Localization
243	256.5±50.7 (19.8)	105.5	Phase I	Nasal Localization
243	243.8±31.7 (13.0)	100.3	Phase I	Ocular Detection

TABLE 2. Concentration of glutaraldehyde in VDD [a]				
Nominal (ppb)	Actual (mean ppb±SD; CV%)	%	Phase	Section
243	266.2±61.1 (22.9)	109.5	Phase I	Nasal Localization
243	246.8±71.5 (29.0)	101.6	Phase I	Nasal Localization
243	262.3±23.3 (8.9)	108.0	Phase I	Ocular Detection
243	235.2±32.0 (13.6)	96.8	Phase I	Nasal Localization
243	247.0±21.4 (8.7)	101.7	Phase I	Nasal Localization
243	266.7±34.5 (12.9)	109.8	Phase I	Ocular Detection
243	266.7±65.1 (24.4)	109.8	Phase I	Nasal Localization
243	259.5±49.5 (19.1)	106.8	Phase I	Ocular Detection
243	242.2±0.2 (0.1)	99.7	Phase I	Nasal Localization
243	272.8±43.3 (15.9)	112.2	Phase I	Nasal Localization
243	240.8±17.8 (7.4)	99.1	Phase I	Ocular Detection
243	252.4±53.8 (21.3)	103.9	Phase I	Ocular Detection
243	232.6±46.3 (19.9)	95.7	Phase I	Nasal Localization
243	251.6±17.4 (6.9)	103.5	Phase I	Ocular Detection
547	498.6±30.8 (6.2)	91.2	Phase I	Ocular Detection
821	724.0±41.8 (5.8)	88.2	Phase I	Ocular Detection
821	798.5±51.9 (6.5)	97.3	Phase I	Nasal Localization
821	690.1±93.1 (13.5)	84.1	Phase I	Ocular Detection
821	754.3±132.3 (17.5)	91.9	Phase I	Ocular Detection
821	694.2±51.0 (7.3)	84.6	Phase I	Ocular Detection
821	773.7±33.8 (4.4)	94.2	Phase I	Ocular Detection
821	728.4±85.3 (11.7)	88.7	Phase I	Ocular Detection
821	687.8±118.0 (17.2)	83.8	Phase I	Nasal Localization
821	729.3±108.2 (14.8)	88.8	Phase I	Nasal Localization
821	670.4±139.0 (20.7)	81.7	Phase I	Nasal Localization
821	714.4±164.5 (23.0)	87.0	Phase I	Ocular Detection
821	721.9±74.6 (10.3)	87.9	Phase I	Nasal Localization
821	761.9±192.9 (25.3)	92.8	Phase I	Nasal Localization
821	707.0±121.4 (17.2)	86.1	Phase I	Ocular Detection
821	814.3±247.6 (30.4)	99.2	Phase I	Nasal Localization
821	672.7±253.9 (37.7)	81.9	Phase I	Nasal Localization
821	764.3±104.7 (13.7)	93.1	Phase I	Ocular Detection
821	771.3±94.5 (13.3)	86.6	Phase I	Nasal Localization
821	739.5±104.5 (14.1)	90.1	Phase I	Nasal Localization
821	688.4±217.2 (31.6)	83.9	Phase I	Ocular Detection
821	727.4±33.8 (4.6)	88.6	Phase I	Nasal Localization
821	759.2±237.2 (31.2)	92.5	Phase I	Ocular Detection
821	569.0±74.2 (13.0)	69.3	Phase I	Nasal Localization
821	700.7±60.1 (8.6)	85.4	Phase I	Nasal Localization
821	663.6±115.7 (17.4)	80.8	Phase I	Ocular Detection
821	636.9±165.4 (26.0)	77.6	Phase I	Ocular Detection
821	740.7±41.2 (5.6)	90.2	Phase I	Nasal Localization
821	707.8±59.3 (8.4)	86.2	Phase I	Ocular Detection

[a] Data derived from pp. 47-69 Table 4 of the study report.

A great deal of variance was observed in the actual concentrations as compared to the nominal concentrations, with 74% (CV=15.2%) for 2.48 ppb; 92% (average CV=9.8%) for 4.95 ppb; 94% (CV=2.5%) for 9.9 ppb; 83% (CV=3.8%) for 72 ppb; 92% (average

CV=5.9%) for 108 ppb; 102% (average CV=14.7%) for 243 ppb; and 87% (average CV=16.1%) for 821 ppb. Dose groups 9.9, 72, 108, 243, and 821 were not in the study protocol. A few nominal concentrations did not correspond to a dose in the protocol as well as 3 of the 7 actual doses ≥10% of the nominal dose.

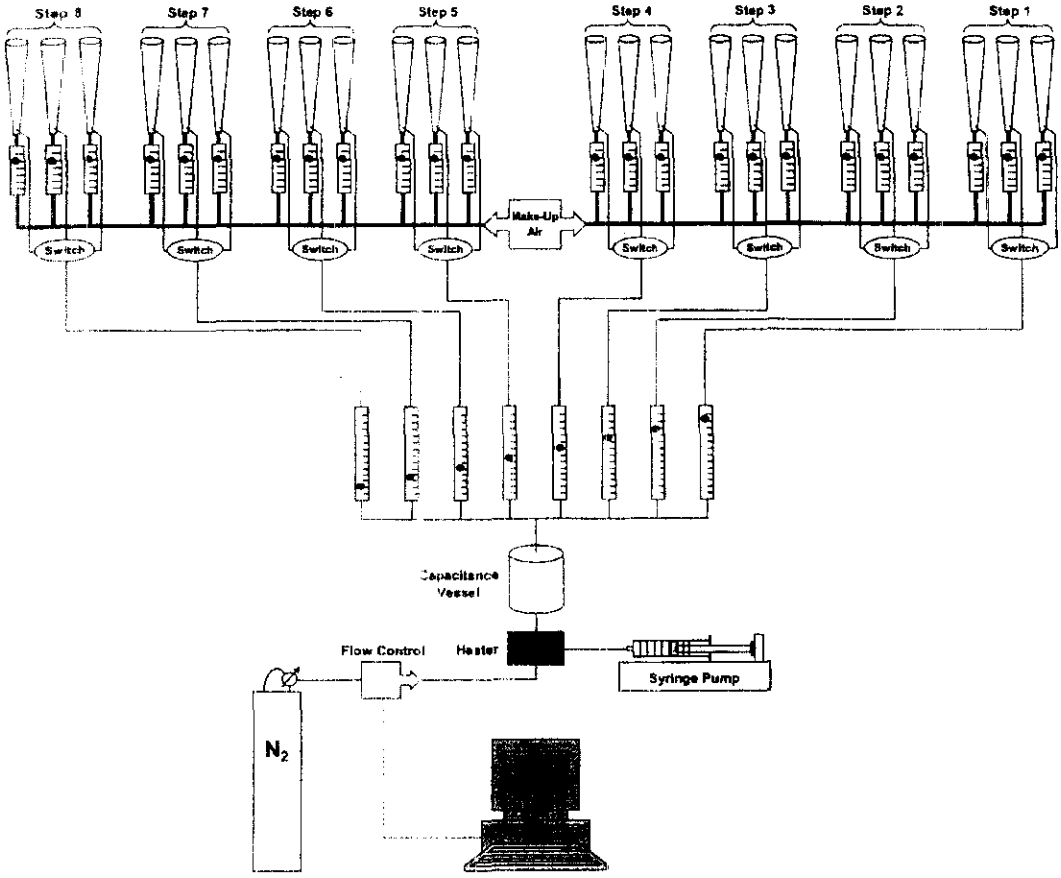

FIGURE 1. Schematic of the VDD (pp. 18 of the study report)

The set up that generated vapor with the cones (VDD) in Phase I also served in Phase II with the environmental chambers. The details of Phase II concentrations were presented in the study report Table 8 (pp. 119-145) with study report Table 9 serving as the summary data for concentration analysis. The environmental chambers over the days of exposure were consistent with the nominal concentrations as summarized in Table 3 below

TABLE 3. Concentration of glutaraldehyde in exposure chambers [a]

Nominal (ppb)	Actual (mean ppb±SD)	CV%	%
35	35.78±5.39	15.07	102
50	52.94±6.82	12.88	106
75	78.97±9.34	11.82	105
100	103.45±7.93	7.67	103

[a] Data derived from study report table 9, p. 147

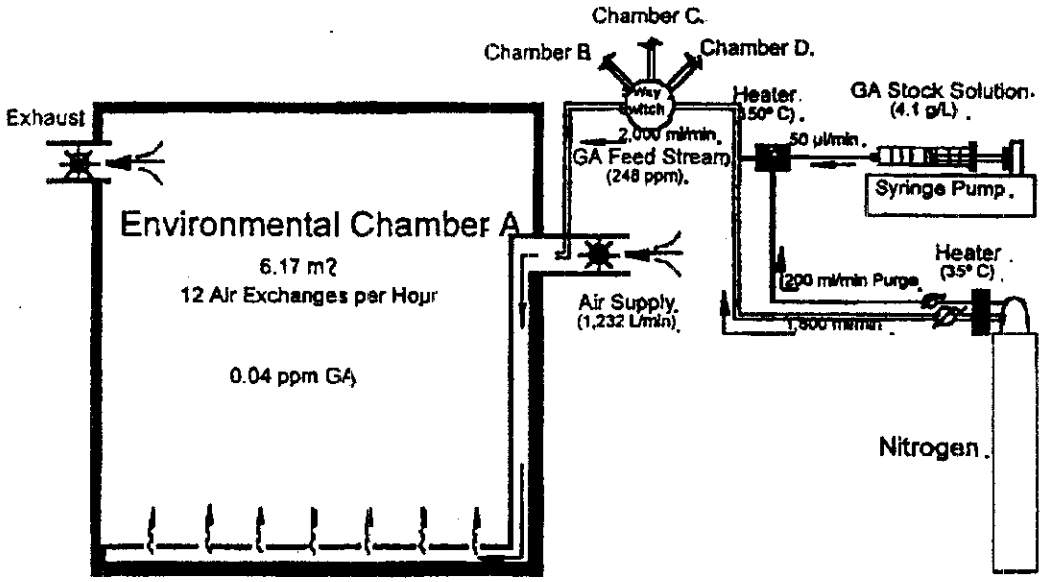

FIGURE 2. Schematic of the exposure chamber (pp. 204 of the study report)

The positive control heptane was used in Phase II. Air was used as a blank.

II. TEST PHASES AND RESULTS:

A. PHASE I DESIGN (TABLE 4)

The first phase addressed the issue of detection to brief (momentary) exposures and consisted of three parameters: odor detection, ocular detection, and nasal lateralization which were each performed separately. Ideally, a subject remained for a full day of testing, which consisted of up to 30 rounds (8 concentrations x 30 rounds = 240 judgments). A typical schedule for subjects enrolled for a full day of testing was 0930 until 1700. During a full day of testing, the subject completed one of the following: up to 30 rounds of odor detection, ocular detection, or nasal localization. The subjects were to identify the scent of glutaraldehyde (both nostrils, single sniff) between 3 cones, 2 blank and 1 active, via a vapor delivery system that produced analytical data of the exposure concentration of glutaraldehyde. The glutaraldehyde concentration increased with each round. Each detection session was 30 seconds in total, with three 5- second sampling periods at each cone. Following exposure, the subject would leave the 3 cones and mark their response to the sniff test on a bubble sheet during a 15 second break till the next round of sampling. Ocular detection involved a 100-second cycle and was evaluated in a similar method as nasal detection with 3 cones of exposure, 1 active and 2 blank cones. During each round, one eye was exposed at each cone for 25 seconds and was followed by the subject's confidence rating. Nose clips were worn in order to prevent nasal stimulation. Only one eye was placed to the face of a cone with the exposed eye being switched from one station to the next. Nasal localization required the subjects to determine if the sensation was on the left or right nostril after a 5 second sampling period with 45 seconds between each sampling. Testing of odor or feel (eye or nasal) required the subject to decide which of the three cones had the strongest odor or feel among two

blanks (air) and one active cone at each station (8 stations total). After the subject sampled each cone, the subject wrote the choice in the appropriate cell on a data sheet carried on a clipboard. The subject was asked do you feel "yes" or "no". The scale of confidence ranged from 1= no confidence to 5 = very high confidence, with a midpoint of 3 = moderate confidence. Severity of feel was not rated in Phase I. The subject completed these judgments before the next trial began. A full round of testing for a subject included eight trials in the ascending order of concentration.

TABLE 4. Test methods and parameters examined in Phase I

Parameter	Female N	Exposure duration	Exposure Concentration (ppb)	# cones	# concen-trations	# rounds	Notes
Odor detection	43	>5 sec	0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, or 4.950	3 cones; 1 active	8	30	1 to 5 scale; no positive control; randomized active cone position; goggle reduce eye contact
Ocular detection	41	25 sec	229, 343, 514, or 772	3 cones; 1 active	4	30	1 to 5 scale; no positive control; randomized active cone position; nose clips to reduce nasal contact
Nasal lateralization	40	>5 sec	229, 343, 514, or 772	2 cones; 1 active	4	30	Each nostril sniffs different cone and determine which cone contains glutaraldehyde

PHASE I RESULTS:

1. Study Report Analysis, odor:

The median concentration as indicated in the study report for the odor of glutaraldehyde (at a point of 50% detection) was 0.3 ppb. Psychometric functions from 4 subjects were presented for odor and ocular and nasal localization in Figure 4 of the report. An analysis of the median was not presented in the report.

Additional AD Analysis, odor.

An independent Antimicrobials Division (AD) analysis indicates 96% (41 of 43) of subjects were capable of detecting odor over the range of concentrations examined. Ten subjects (23%) initially detected at 0.039 ppb and consistently to the highest concentration of 4.94 ppb. Two subjects (4.6%) failed to detect odor at any concentration. Using a simple tally method, the 50th percentile of the distribution of 'true detectors' is the 21.5th observation of the 43 persons detecting the chemical, or 0.15 ppb. The tally of the subjects' initially and consistently detecting odor is presented in Table 5.

Table 5. Tally of subjects initially and consistently detecting odor of glutaraldehyde

TABLE 5: Glutaraldehyde odor detection (Phase I)				
Dose Level (ppb)	**Initially & Consistently Detecting Subjects**	**Total Subjects**	**Percent Detect**	**Running Total % Detecting**
0.039	10	43	23	23
0.077	7	43	16	39
0.15	6	43	14	53
0.31	2	43	5	58
0.62	9	43	21	79
1.24	2	43	5	84
2.48	3	43	7	91
4.95	2	43	5	96
Non-detecting	2	43	5	100
Total	43	43	100	--

2. Study Report Analysis, Eye:

The median at which subjects detected glutaraldehyde in the eye 50% of the time was 390 ppb. This analysis of the median was not presented in the report.

Additional AD Analysis, Eye:

An AD analysis indicates approximately 39% (16 of 41) of subjects positively identified eye feel beyond chance initially at 229 ppb and consistently to 772 ppb. One subject failed to detect eye feel up to 772 ppb. However, 98% (10 of 41) identified glutaraldehyde in the eye at 772 ppb. The 50th percentile is 343 ppb based on the simple tally method. The tally of the subjects' initially and consistently detecting eye chemesthesis is presented in Table 6.

Table 6. Tally of subjects initially and consistently detecting ocular feel of glutaraldehyde

TABLE 6: Glutaraldehyde eye detection (Phase I)				
Dose Level (ppb)	**Initially & Consistently Detecting Subjects**	**Total Participants**	**Percent Detect**	**Running Total % Detecting**
229	16	41	39	39
343	13	41	32	71
514	5	41	12	83
772	6	41	15	98

Non-detecting	1	41	2	100
Total	41	41	100	--

3. Study Report Analysis, Nasal:

The median at which subjects detected glutaraldehyde in the nose 50% of the time was 470 ppb. This analysis of the median was not presented in the report.

Additional AD Analysis, Nasal:

An AD analysis indicates 77.5% (31 of 40) of subjects positively identified glutaraldehyde in the nose at the lowest concentration of 229 ppb. All subjects identified glutaraldehyde in the nose at 772 ppb. The 50th percentile is therefore 229 ppb. It should be noted that although all subjects could detect the feel of glutaraldehyde in the nose at some concentration in the study, the subjects failed to identify which nostril was being exposed. The tally of the subjects' initially and consistently detecting nose chemesthesis is presented in Table 7.

Table 7. Tally of subjects initially and consistently detecting nasal feel of glutaraldehyde

TABLE 7: Glutaraldehyde nasal detection (Phase I)				
Dose Level (ppb)	**Initially & Consistently Detecting Subjects**	**Total Participants**	**Percent Detect**	**Running Total % Detecting**
229	31	40	77.5	77.5
343	3	40	7.5	85
514	4	40	10	95
772	2	40	5	100
Non-detecting	0	40	0	--
Total	40	40	100	--

For Phase I, odor was 3 orders of magnitude more sensitive than eye and nasal detection. Although odor was most sensitive to female subjects, nasal chemesthesis appeared to be more sensitive than eye chemesthesis. Subjects failed to lateralize (left or right) feeling of glutaraldehyde in the nose.

TABLE 8. Summary of Phase 1 results for odor, eye, and nasal threshold of glutaraldehyde				
Exposure Concentration	**Exposure Duration**	**Number of Participants**	**Median Threshold in Report**	**AD Independent Analysis**
Odor Detection				
0, 0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, and 4.950 ppb	>5 seconds "sniff"	43	Odor median 0.3 ppb	23% at 0.039 ppb (10 of 43); 2 non-detecting; Median 0.15 ppb
Ocular Feel				
0, 229, 343, 514, and 772 ppb	25 seconds	41	Ocular median 390 ppb	39% at 229 ppb (16 of 41); 1 non-detecting; Median 343 ppb
Nasal Localization				
0, 229, 343, 514, and 772 ppb	>5 seconds "sniff"	40	Nasal median 470 ppb*	77.5% at 229 ppb (31 of 40); 0 non-detecting; Median 229 ppb

B. PHASE II DESIGN (TABLE 9):

The goal of the second phase was to establish the effect of time on sensitivity. The second phase consisted of 15 minute exposures in a walk-in chamber. The daily exposure regime consisted of two exposures to air, two exposures to 10 ppm heptane used as an odor control, and one exposure each to 0, 35, 50, 75, and 100 ppb glutaraldehyde vapor. The first exposure in a day consisted of a known blank (air), in order to serve as an acclimation to the task in the chamber (practice run). The subjects made ratings as they would for the subsequent blinded exposures.

In this study, one subgroup of 25 subjects was exposed to glutaraldehyde in an ascending order, intermixed with blanks and odor controls, while the other subgroup of 25 subjects was exposed to glutaraldehyde in a descending order (Table 9). The study report did not indicate if the subjects were aware of the schedule for a day of testing. Subjects were allowed 45 to 75 minutes between exposures to glutaraldehyde. This phase examined the subject's response to the feel of glutaraldehyde in the eyes, nose, and throat over time.

TABLE 9. Period and concentration for Phase 2				
Parameter	**Females (N)**	**Parameter**	**Females (N)**	**Exposure Duration (minutes)**
blank blinded (air)[a]	25	blank blinded	25	15
10 ppm n-heptane	25	10 ppm n-heptane	25	15
35 ppb glutaraldehyde	25	100 ppb glutaraldehyde	25	15
50 ppb glutaraldehyde	25	75 ppb glutaraldehyde	25	15
75 ppb glutaraldehyde	25	50 ppb glutaraldehyde	25	15
10 ppm n-heptane	25	10 ppm n-heptane	25	15
100 ppb glutaraldehyde	25	35 ppb glutaraldehyde	25	15

[a]A second blank blinded (air) sample was reportedly administered to the test subjects; however, the timing of this sample was not described in the study report or any accompanying tables.

Before the subjects entered the chamber, the investigator explained that the task inside the chamber would entail judgments of confidence that certain sensory events were occurring at sixteen closely-spaced periods of time during 15 minute exposures. The response was then "yes" for a positive feel or "no" for no feel. Additionally, the subject needed to attach a level of confidence to each event (nose, eye, and throat). The score rating was 1 = not certain, 2 = moderately certain, and 3 = very certain. For example, if a subject detected nothing at all in the nose. the rating was "no" and "3" for no detection and very certain. Additionally, it should be noted that odor was not a parameter evaluated in this phase of the study.

Study Analysis for Phase 2:

The confidence scores of 1 to 3 were entered as -1 to -3 for "no" judgments and as +1 to +3 for "yes" judgments. This transformed into a scale of 1 to 6, with 1 to 3 describing the -1 to -3 scores, and 4 to 6 describing the +1 to +3 scores, for a total of 6 points. The midpoint of 3.5 indicated the demarcation between "no" and "yes". The scale of 1 to 6 lent itself to ANOVA on the assumption of interval scale measurement. It should be noted, however, that the transformation of the data from a "no" or "yes" judgement to a total of 6 points (1 to 6) was not included in the appendices of the report. Verification of the ANOVA analysis was not possible. Tables 13-27 (page 151-186) present the individual subject data (Phase II) as confidence ratings -1 to -3 and +1 to +3 for the heptane control as well as the 35, 50, 75, and 100 ppb glutaraldehyde. The subjects' responses to the blank (air) at two different trials were not included in the report.

PHASE II RESULTS:

Study Report Results:

ANOVA results provided in the study report indicated level (i.e., concentration) of exposure had stronger effects on the nose than the eye and the eye more than on the throat, though significance was achieved for effects on all three parameters (Table 10). In general, each site exhibited its own pattern; however, no site demonstrated a dose-response relationship. Significance for the interaction of level by duration, as seen by rated confidence, was achieved for the nose only. This result suggested that confidence did not increase faster for the various dose levels of glutaraldehyde as compared to the blank in the eye and the throat.

TABLE 10. ANOVA results of effect of level and time by exposure site[a]			
Parameter	**Site**	**ANOVA F-test Result**	**Level of Significance**
Level	Eye	F[4,196] = 6.59	p<0.0001
	Nose	F[4,196] = 12.52	p<0.0001
	Throat	F[4,196] = 3.68	p<0.007
Duration	Eye	F[15,735] = 27.0	p<0.0001
	Nose	F[15,735] = 15.09	p<0.0001
	Throat	F[15,735] = 25.52	p<0.0001
Interaction between Level and Duration	Eye	F[60,2940] = 1.18	Not Significant
	Nose	F[60,2940] = 2.29	P<0.01
	Throat	F[60,2940] = 1.12	Not Significant

[a]Results taken from pp. 29 of the study report.

While the rated confidence for the nose did increase faster at the different levels of glutaraldehyde as compared to the blank, there was no indication at any site of the average rating of confidence transitioning from "no" to "yes" or of the aggregate number of a "yes" response exceeding 50%. This suggested that subjects possessed little certainty regarding the presence of feel from the exposure.

An aggregate of the ratings by site was conducted by using the highest rating during glutaraldehyde exposure and the corresponding rating during blank exposure for each point in time and subject. For example, if a subject rated the nose higher than the throat and eye, the rating for the nose would go into the aggregate. If two or more ratings were tied for the highest, an average of the corresponding blanks was taken to include in the aggregate tally. The results in Table 11 from the functions for the aggregates indicated that at most a minor dose-response relationship may have been observed for exposures up to 75 ppb. Additionally, the ratings for glutaraldehyde consistently exceeded that for the respective blank comparisons (could not be verified by the Agency).

TABLE 11. ANOVA results for the ratings of glutaraldehyde exposure compared to the blank[a]		
Glutaraldehyde Concentration	**ANOVA F-test Result**	**Level of Significance**
35 ppb	F[1,49] = 47.76	p<0.0001
50 ppb	F[1,49] = 59.93	p<0.0001
75 ppb	F[1,49] = 54.93	p<0.0001
100 ppb	F[1,49] = 42.61	p<0.0001

[a]Results taken from p. 30 of the study report.

However, the analysis for the interaction of time by exposure (Table 12) suggests that significance was only achieved at 50 and 75 ppb. Consequently, the results demonstrated

no dose-dependent tendency for judgments during glutaraldehyde exposures to indicate temporal integration.

TABLE 12. ANOVA results for the interaction of time by exposure[a]		
Glutaraldehyde Concentration	**ANOVA F-test Result**	**Level of Significance**
35 ppb	F[15,735] = 1.64	Not Significant
50 ppb	F[15,735] = 2.61	p<0.001
75 ppb	F[15,735] = 3.71	p<0.0001
100 ppb	F[15,735] = 0.57	Not Significant

[a]Results taken from p. 31 of the study report.

AD Independent Analysis:

Binary detection indicators (yes/no) were combined by participant across dose levels (see Appendix A). Similar to the Phase I analysis, AD determined the level at which each participant initially and consistently detected glutaraldehyde. In Phase II, a significant proportion of participants could not detect glutaraldehyde at any concentration. For example, using eye irritation as a marker of detection of the chemical, 43 of the 50 (86%) participants could not detect the chemical (Table 13). Two subjects, however, detected eye irritation initially at 35 ppb and consistently to 100 ppb. For nasal irritation, 33 of 50 (66%) could not detect at any concentration while 5 subjects detected initially and consistently (Table 14). For throat irritation, 42 of 50 (84%) failed to detect over the range of concentrations while 4 subjects did so initially at 35 ppb and consistently to 100 ppb (Table 15). Only 1 subject responded initially at the lowest concentration and consistently to the highest concentration for all three sites, eye, nose, and throat.

Table 13: Glutaraldehyde Eye Confidence (Phase II)				
Concentration (ppb)	**# subjects initially & consistently detecting**	**Total**	**Percent Detect**	**Adjusted**
35	2	7	29	
50	1	7	14	
75	0	7	0	
100	4	7	57	
Total	7	--	100	0
>100 (not detect)	43	50	86	0

Table 14: Glutaraldehyde Nasal Confidence (Phase II)				
Concentration (ppb)	**# subjects initially & consistently detecting**	**Total**	**Percent Detect**	**Adjusted**
35	5	17	29	
50	2	17	12	
75	4	17	24	
100	6	17	35	
Total	17	--	100	0
>100 (not detect)	33	50	66	0

Table 15: Glutaraldehyde Throat Confidence (Phase II)				
Concentration (ppb)	# subjects initially & consistently detecting	Total	Percent Detect	Adjusted
35	4	8	50	
50	1	8	13	
75	0	8	0	
100	3	8	37	
Total	8	--	100	0
>100 (not detect)	42	50	84	0

In summary, female subjects generally failed to positively detect glutaraldehyde either in the eyes, nose, or throat over the concentrations and duration (15 minutes) investigated. As a group, there was no concentration-response relationship for the eyes, nose, or throat. Examination of the confidence scores suggests that the nose may be more sensitive than the eyes which may be more sensitive than the throat, which is consistent with findings in Phase I. A concentration that 50% of the subjects could detect (eye, nose, or throat) was not identified. **A LOAEL was not established in this phase. The NOAEL for perception of irritation after 15 minutes is > 100 ppb.**

III. SUMMARY OF THE 2 PHASES:

TABLE 16. Summary table of glutaraldehyde odor detection and eye, nose, and throat irritation in healthy subjects			
Phase	Exposure Concentration	Exposure Duration	Results
Phase I: odor detection	0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, and 4.950 ppb	>5 seconds	• Odor median = 0.15 ppb • 23% subjects detected at 0.039 ppb (10 of 43) • 2 non-detecting subjects
Phase I: ocular detection	229, 343, 514, and 772 ppb	25 seconds	• Median 343 ppb • 39% subjects detected at 229 ppb (16 of 41); • 1 non-detecting subject
Phase I: Nasal Chemesthesis	229, 343, 514, and 772 ppb	>5 seconds	• Median 229 ppb • 77.5% at 229 ppb (31 of 40) • 0 subjects failed to detect
Phase II	35, 50, 75, and 100 ppb	15 minutes	• 86% (43 of 50) failed to detect eye irritation • 66% (33 of 50) failed to detect nasal irritation • 84% (42 of 50) failed to detect throat irritation
Phase III	Not conducted		

IV. DISCUSSION:

A. SUBJECT SELECTION DISCUSSION

Phase I and Phase II only used females. While justification for the use of only females was provided in the study report, testing both sexes would have been useful in determining that no sex differences are found in glutaraldehyde odor and chemesthesis detection.

B. PHASE I DISCUSSION

Phase I of the study provided descriptive data on the odor, eye, and nasal detection threshold. In addition, this phase provides odor, eye, and nasal detection medians based either on a group level or on a more refined level (i.e., consistently and continuously detecting). Variability is evident in the subject's ability to detect glutaraldehyde over the range of concentrations. Detection was based on a subjective confidence scores with no severity scores or physiological parameters to further inform the response to glutaraldehyde. Another uncertainty from this phase of the study is the possible variability of a subjects' response on different testing days. The data are adequate in determining the threshold of detection.

C. PHASE II DISCUSSION

Phase II involved a more realistic exposure scenario than Phase I for informing an acute exposure scenario. Severity or pungency of the feel of glutaraldehyde exposure, however, was not included in this phase of the study. Although a high confidence of feel to glutaraldehyde may indicate a level of severity, this comparison can not be made in this phase

The design of the study did follow a low to high concentration exposure scenario. All statistics performed by the Chemosensory Perception Laboratory were based on a group level. However, the response to glutaraldehyde is important both on a group and individual scale. Analysis on an individual level provides the number of subjects able to detect glutaraldehyde with confidence compared to those subjects not detecting at any concentration. Since all testing was to be completed in one day, a parameter or question to address any effects that may still be residual from the previous exposure period would have been helpful. Confidence scores of the first few minutes of each testing period, however, reveal low confidence scores of feel. These low confidence scores at the beginning of each testing period suggest that no residual effects were present from the previous period.

D. OVERALL DISCUSSION

The lack of a Phase III and clinical measures of irritation decreases the utility of this study. Odor detection and feel detection could protect against irritation, but without physiological evidence of precursors to irritation, this study only describes sensation and odor thresholds. Furthermore, subjective measures of severity or pungency were not measured. However, a dose-response in detection was not observed in Phase I, indicating that saturation of the olfactory nerve could be achieved at a low concentration for glutaraldehyde. Lateralization thresholds were not able to be determined because the subjects were unable to localize glutaraldehyde in their nostrils, indicating that at the concentrations tested irritation was not achieved. This study is a range-finding study to determine exposure scenarios for an irritation study of glutaraldehyde on human subjects.

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Appendix A

Statistical Analysis of Phase I and Phase II of the Glutaraldehyde Human Irritation Study. 2006. Nikki Maples Reynolds and Ami Parekh, ICF International

Human Eye Irritation and Odor Threshold Study

The Chemosensory Perception Laboratory of the University of California, San Diego performed a non-guideline, special study to determine the sensitivity of participants to glutaraldehyde through both direct and indirect exposure. Phase I established the sensitivity of participants to the chemical through exposure applied directly to the organ of interest, i.e., eye or nose, using specifically designed exposure equipment (3 cones). Phase II ascertained the sensitivity of test participants to glutaraldehyde through indirect exposure in a full-body chamber. In Phase II, researchers were to investigate irritation of the eye, nose, and throat through ambient exposure to glutaraldehyde. Phase III of the study was not conducted. The Phase II dosing scenario is the exposure scenario that best approximates that which will be encountered by workers and bystanders and is the exposure scenario that is of most interest to OPP. A statistical analysis of the submitted raw data was performed to determine the distribution of glutaraldehyde detection levels through eye irritation and odor sensation in Phase I and Phase II of the "odor and chemesthesis form exposures to glutaraldehyde vapor." Our methods were different than the Chemosensory Perception Laboratory of the University of California, San Diego, in that for Phase I, the statistics AD employed took into account the number of choices and correcting for guessing correctly. Therefore, our results differ from that of the Chemosensory Perception Laboratory of the University of California, San Diego.

Phase I

In Phase I, participants experienced brief (>5 second) contact with glutaraldehyde through direct ocular and nasal exposure using specially made exposure devices. Each of the participants was asked to judge whether the chemical was present in approximately 30 (27-30) trials for each of 8 dose levels (0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, or 4.950 ppb). Each trial consisted of three 'cones' or exposure devices, one of which contained glutaraldehyde. In each trial, participants recorded which exposure device contained glutaraldehyde based upon sensation or irritation to the nose (odor detection) and eye, respectively. There were 43 participants who completed the odor detection portion and 41 participants who completed the eye feel portion of Phase I. Nasal feel was determined in 40 subjects. These data provide the basis for the distribution describing glutaraldehyde detection in the sample.

To perform this task, the investigators recorded the number of positive detections (a participant's judgment that the chemical is present in the exposure device) as a proportion of the total number of trials and 'corrected' this proportion to reflect the proportion of positive detections required to consider an individual participant to have positively detected the chemical beyond chance at each dose level. An individual participant may correctly determine the presence of the chemical in the exposure device in some of the trials by chance or pure guess. By 'correcting' for participants' chance occurrence of a

positive detection of the chemical, a distribution of detection levels which reflects the true dose levels at which participants are able to detect the chemical through eye or nasal feel or odor detection was created. It should be noted, however, that this analysis did not address the possible influence of a participant's variability in detection over different days of participation. For example, some subjects performed all trials in one day whereas other subjects performed the total trials over a 4 day period.

AD utilized a scoring method similar to that used in some multiple choice exams to remove the effect of chance or guessing while recording of total number of positive detections. The following algorithm is used to determine the score for each study participant:

Score = total # positive detections - 0.5 (total # trials - total # positive detections)

Given an individual participant's score, that participant is classified as either a 'true detector' or a 'non-detector' (1 or 0, respectively) for each of the four dose levels using the criterion:

Detect=1 if Score>0.33(# correct detects)
Detect=0 if Score#0.33(# correct detects)

In Phase I, participants were also asked to provide a confidence score at each trial. Participants rated their assurance on a scale of 1-5 reflecting how confident they were that the glutaraldehyde was or was not in the exposure device. This information was not incorporated or otherwise considered in this analysis, nor was it presented in the study report or apart of the Chemosensory Perception Laboratory of the University of California, San Diego statistical analysis.

The next step is to determine the dose level at which each participant in the study initially and continuously detected the chemical. To do this, a rule was placed on the data: participants were not allowed to be scored as 'true detectors' at one dose level and 'non-detectors' at a higher dose level. There is no biological reason to assume some participants would be able to detect glutaraldehyde at a low dose level but not be able to detect glutaraldehyde at a higher dose level. Therefore, some alterations were made to the data set to reflect the amended criterion:

Detect=1 if Score>0.33(# correct detects)
Detect=0 if Score#0.33(# correct detects)

Non-Monotonic
The amended criterion ensures each participant was a monotonically increasing or constant glutaraldehyde non-detector or detector across the increasing dose levels of Phase I (odor detection: 0.039, 0.077, 0.150, 0.310, 0.620, 1.240, 2.480, or 4.950 ppb; ocular and nasal feel: 229, 343, 514, or 772 ppb). The tables below enumerate the total number of participants who initially and continuously detected the chemical at each of

the eight dose levels in both the odor detection (Table A1), eye irritation (Table A2, and nasal irritation parts (Table A3) of Phase I.

TABLE A1: Glutaraldehyde odor detection (Phase I)

Dose Level (ppb)	Initially & Consistently Detecting Subjects	Total Subjects	Percent Detect	Running Total % Detecting
0.039	10	43	23	23
0.077	7	43	16	39
0.15	6	43	14	53
0.31	2	43	5	58
0.62	9	43	21	79
1.24	2	43	5	84
2.48	3	43	7	91
4.95	2	43	5	96
Non-detecting	2	43	5	100
Total	43	43	100	--

TABLE A2: Glutaraldehyde eye detection (Phase I)

Dose Level (ppb)	Initially & Consistently Detecting Subjects	Total Participants	Percent Detect	Running Total % Detecting
229	16	41	39	39
343	13	41	32	71
514	5	41	12	83
772	6	41	15	98
Non-detecting	1	41	2	100
Total	41	41	100	--

TABLE A3: Glutaraldehyde nasal detection (Phase I)				
Dose Level (ppb)	Initially & Consistently Detecting Subjects	Total Participants	Percent Detect	Running Total % Detecting
229	31	40	77.5	77.5
343	3	40	7.5	85
514	4	40	10	95
772	2	40	5	100
Non-detecting	0	40	0	--
Total	40	40	100	--

Phase II

In Phase II of the study, participants entered a whole-body (ambient) exposure chamber and were exposed to glutaraldehyde over a 15-minute exposure interval. The four dose levels investigated in this phase of the glutaraldehyde human study were 35, 50, 75 or, 100 ppb. For each dose level, participants assessed whether glutaraldehyde was present in the chamber using a 6-point scale. However, this 6-point scale was not reported in the Tables of the study report. Alternatively, the data were reported as a "no" response if "-1, -2, or -3" and "yes" response if "+1, +2, or +3" reflected both the participants' judgment as to whether or not the chemical was present in the chamber as well as a level of confidence in the judgment. Participants assessed whether the chemical was present in the chamber based on the level of irritation to the eye, nose, and throat at 30 seconds, 1-minute and each minute thereafter that participants remained in the whole-body chamber. For example, if an individual rates the presence of the glutaraldehyde in the chamber at minute 9 with a score of 2, that participant believes the chemical is present due to irritation symptoms to eye, nose, or throat with a moderate level of confidence at minute 9 of the 15 minute exposure period.

AD classified each participant as to whether or not the participant could detect the chemical during each of the exposure periods. In this analysis, AD defined a 'true detector' as a participant who detected the chemical in the exposure chamber with an irritation confidence level of 2 or 3 in any 2 or more exposure minutes during the 15 minute exposure period. Therefore, participants who gave confidence scores of -1, -2, -3, or +1 throughout the time period in the chamber were considered non-detectors and participants who gave confidence scores of 2 or 3 at least two time points in the exposure interval were considered detectors. The heptane control responses were not included in this analysis and the blank (air) responses were not provided and therefore also not included in the analysis.

Binary detection indicators (yes/no) were combined by participant across dose levels. Similar to the Phase I analysis, AD determined the level at which each participant initially and consistently detected glutaraldehyde. In Phase II, a significant proportion of participants could not detect glutaraldehyde at any concentration. For example, using eye irritation as a marker of detection of the chemical, 43 of the 50 participants could not

detect the chemical. Furthermore, 33 and 42 participants among 50 could not detect the chemical by nasal or throat irritation symptoms, respectively. Only 1 subject responded initially at the lowest concentration and consistently to the highest concentration for all three sites, eye, nose, and throat.

Table A4: Glutaraldehyde Eye Confidence (Phase II)				
Concentration (ppb)	**# subjects initially & consistently detecting**	**Total**	**Percent Detect**	**Adjusted**
35	2	7	29	
50	1	7	14	
75	0	7	0	
100	4	7	57	
Total	7	--	100	0
>100 (not detect)	43	50	86	0

Table A5: Glutaraldehyde Nasal Confidence (Phase II)				
Concentration (ppb)	**# subjects initially & consistently detecting**	**Total**	**Percent Detect**	**Adjusted**
35	5	17	29	
50	2	17	12	
75	4	17	24	
100	6	17	35	
Total	17	--	100	0
>100 (not detect)	33	50	66	0

Table A6: Glutaraldehyde Throat Confidence (Phase II)				
Concentration (ppb)	**# subjects initially & consistently detecting**	**Total**	**Percent Detect**	**Adjusted**
35	4	8	50	
50	1	8	13	
75	0	8	0	
100	3	8	37	
Total	8	--	100	0
>100 (not detect)	42	50	84	0

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Chemical: Glutaraldehyde

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